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The large grey area between ‘bona fide’ and ‘rogue’ stem cell interventions — Ethical acceptability and the need to include local variability☆



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ABSTRACT

This article aims to put into perspective the binary opposition between ‘scientific’ clinical research trials and ‘rogue’ experimental stem cell therapies, and to show why the ethics criteria used by the dominant science community are not suitable for distinguishing between adequate and inadequate treatments. By focusing on the grey area between clinical stem cell trials and stem cell experimentation, the experimental space where patients, medical professionals and life scientists negotiate for diverging reasons and aims, I show why idealised notions of ethics are not feasible for many stem cell scientists in low- and middle-income countries.

Drawing on fieldwork in China from 2012 to 2013, the article asks why ‘the unethical’ according to some is acceptable to Chinese life scientists. The case study of stem cell service provider Beike Biotech illustrates how stem cell interventions take place in a large grey area, where narrow notions of ethics are blurred with and supplanted by broader notions of ethics, co-determined by estimations of socio-economic, political and cultural understandings of risk, opportunity and benefit.

I borrow the term ‘bionetworking’, understood as the entrepreneurial aspects of scientific networks that engage in creating biomedical products, to analyse various forms of medical experimentation. I speak of the ‘externalisation’ and ‘internalisation’ of local factors to elucidate how features of patient populations and their environments are subsumed in clinical research applications. Compared to polarised views of stem cell therapy, this approach increases the transparency of clinical interventions and broadens our understanding of why ‘stem cell tourism’ to some is ‘stem cell therapy’ to others.

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1. Introduction

In the context of ‘stem cell tourism’, scientists and observers of ethics have made sharp distinctions between randomised controlled trials (RCTs) and ‘experimental’ stem cell therapy provision. Various forms and practices of stem cell research and therapy have been criticised, reported and analysed by social scientists and the press (e.g., McMahon and Thorsteinsdóttir, 2010; The Economist, 2002; Sipp, 2011; Main et al., 2014; Ogbogu et al. 2013; Cyranoski, 2012). Governments in the US, Hungary, the Netherlands, Germany, Ireland, Belize and elsewhere have closed down clinics that provide ‘unauthorised’ stem cell therapies, while others fail to stop stem cell providers from charging high fees to administer ‘unproven therapies’ (Sipp 2009). The distinctions between ‘legitimate’ and ‘illegitimate’, ‘evidence-based’ and ‘traditional’, and

‘science-based’ and ‘experimental stem cell therapies’ are subject to heated discussion among established scientists and critics. These distinctions presume that clinical stem cell interventions that are ‘unproven’ are applied only by quacks (Bharadwaj, 2013): not with the aim to cure disease, but to exploit innocent victims.

Some works on the clinical application of stem cells in LMICs have emphasised the importance of analysing regenerative medicine in the context of globalisation, global politics and global governance (Webster, 2013; Zhang, 2012; Bharadwaj, 2013; Chen and Gottweis, 2013; Sleeboom-Faulkner and Patra, 2011; Sleeboom-Faulkner, 2014). These and others (Salter et al., 2015) have especially focused on the central role of bioethics in the global hegemony of ‘Western’ stem cell science, whereby bioethics and stem cell governance have become a pawn in a global race. Rather than making another claim about the global hegemony of ‘Western’ bioethics, I aim to identify how bioethics is understood in the light of local conditions. I do this by contrasting the local socio-economic, cultural and political factors that are important in the appreciation of clinical stem cell applications, and by exploring a way to relate the polarising and normative discussions of research ethics mentioned above to local factors relevant to the bionetworks, explained in the section below.

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Joseph Coates pointed out that we lack an adequate ethical framework for relations between institutions, and that raising ethical issues in an institutional context can confuse the issues that cannot be subsumed in terms of ethical guidelines (Coates, 1994). Thus, a narrow focus on a narrow definition of ethics has made medical fees, medical ethics and scientific research fraud central to thinking about ‘rogue’ experimental stem cell provision (Sipp 2009; McMahon and Thorsteinsdóttir, 2010; Sipp, 2011; Main et al., 2014; Ogbogu et al. 2013; Cauldfield, 2015). But generalising and preconceived notions of global inequality, exploitation, and human experimentation on the poor and desperate fail to take into account the variability of their institutional embedding: they are unable to capture the significance of the active roles of patients, scientists and governments that facilitate innovative clinical stem cell applications in low- and middle-income countries (LMICs). The ethics of stem cell interventions, then, need to be understood in the socio-economic context in which its gains meaning, significance and is implemented. Rather than doing away with ethics, or understanding the ethics of stem cell applications in terms of ‘rogue’ and bona fide, this approach leads to a more realistic estimation of the meaning of ‘international ethics’ and the reasons for its lack of implementation.

Accounts of local factors underlying such applications are needed to nuance the binary that has been created between ‘good’ RCTs and ‘rogue’ stem cell experimentation (SCE) (see Table 1).

In practice, most forms of clinical stem cell research feature a combination of these ideal-typical features, enabled by the various experimental spaces available in countries globally (Sleeboom-Faulkner et al., 2016). By putting this binary into perspective this article tries to move beyond the view that good clinical practice is a matter of money, ethics and evidence-based science. Instead, it emphasises the importance of local factors that structure the exchanges between patients and research enterprises in shaping the clinical stem cell interventions that take place. This shift of focus from a narrow approach to ethics to value realisation through exchange networks in the life sciences increases the number of factors relevant to the ethics underlying the development and practice of clinical stem cell applications.

1.1. Bionetworking

In clinical stem cell research and its applications the value of scientific knowledge, medical skills, management and materials (including laboratories, assays, serums and biologics) are realised through many kinds of knowledge and material exchanges. They are expressed in a range of commercial and trading assets, including iPR, product licencing, accreditations and scientific collaborations, and materialised in the trade of equipment and biomaterials, and clinical services. Value realisation here (Birch and Tyfield, 2012) requires the strategic deployment of a range of socioeconomic relationships, entailing entrepreneurial skills, planning and management (Jones et al., 2011). While the wellbeing of the patient may be central to scientists’ concerns, it is clear that there are many other factors that condition their ability to sustain their work successfully, be it in an academic department, a company or a clinic. Central to value realisation in the life sciences is the way in which exchanges are positioned in strategic networks shaped through socioeconomic, political-legal and cultural factors, or, ‘bionetworking’

(Sleeboom-Faulkner and Patra, 2011), also involving a myriad of non-scientific activities, including networking, lobbying, managing, trading, and collaborating to produce science. These activities encompass interactions with a wide variety of stakeholders and institutions, ranging from political agencies, corporate sponsors and subsidiary companies to patient groups, local hospitals, universities, and the media. Such ‘bionetworking’ activities, according to Sleeboom-Faulkner and Patra, can be used to justify, prepare, and realise life science research and its applications in marked localities, incentivised not just by the promise of scientific results, but also by the demand of clients, collaborative partners, funding providers and by the development of new knowledge assets (Sleeboom-Faulkner and Patra, 2011). The value realisation in bionetworks differs from the notion of biovalue, which pertains to the yield of vitality produced by the biotechnical reformulation of living processes (Waldby, 2002). Bionetworking refers to social entrepreneurial network activities involving biomedical research and healthcare institutions that respond to health demands and needs (Patra and Sleeboom-Faulkner 2009). A bionetwork consists of a plurality of actors engaged in ‘biotechnical ventures’ (Waldby and Mitchell 2007) working across geographical spaces, regulatory regimes and social institutions. Bionetworks relate to the entrepreneurial aspects of biomedicine, and the strategic use of the differences and similarities in the provision of healthcare, levels of wealth, standards of scientific development, and research regulatory regimes and their implementation (Sleeboom-Faulkner and Patra, 2011). The notion applies to translational scientists working with research budgets financed by the state, as well as to those working on a commercial basis.

1.2. The local shaping of clinical interventions

This article tries to shed light on the distinction between RCTs and SCE in terms of bionetworking, taking into consideration what I refer to as the internalisation and externalisation of local factors; it aims to understand the merits of clinical stem cell interventions, rather than projecting a narrow definition of bioethics onto the field. Some scientific approaches to clinical interventions, such as RCTs, emphasise the generation of scientific value rather than the value of immediate cures (Main et al., 2014). A scientific approach would translate ‘local’ circumstances intervening with a clinical trial as external factors for the purpose of creating generalizable knowledge. It presumes that, only on the basis of such generalizable knowledge, science can serve the creation of efficacious therapy in the long run. This bracketing of local particularity externalises factors that define the patients and their environments as potentially intervening with the aim of universal applicability of the therapeutic product (Will and Moreira, 2010). Although RCTs are usually regarded as a case in point, clinical research methods of lesser pretence also externalise local factors. For instance, the absence of Western medical knowledge among ‘subjects’ at a medical research site in, say Somalia, can be remedied – externalised – by providing research participants with training and instructions regarding the kind of hygiene required, or by temporarily housing research participants in a clinic that conforms to the ideal environment for the experimental research. It is also possible, on the other hand, to utilise the local factors that define patients and their environments to facilitate the local applicability of a therapeutic product: to internalise local factors. For instance, researchers, including those linked with RCTs, might target populations that are ‘medically naïve’, or populations that have a particular genetic or epidemiological profile. Researchers are also interested in populations with rare diseases, incurable diseases and populations that have no alternative healthcare options. Members of all of these populations can become targets for clinical interventions, and in all of these cases the aims of the intervention may be multiple, and can, in principle, include the acquisition of research results, profit, biomaterials, experience, and the expression of compassion and duty. Thus, depending on the context and arrangements made, the application of clinical interventions are decided not only on the basis of disease conditions,

Table 1
The binary between RCT and SCE.

	RCT	SCE
Reliability	Bona fide	Rogue
Quality practice	GMP, GLP, GCP	Dubious
Ethics	Informed consent, IRB	Dishonest, no oversight
Quality results	Scientific, evidence-based	Unscientific
Benefit	For humanity	Exploitative
Procedures	Scientific protocol	Experimental
Knowledge	Generalizable	Inadequate

but also on other factors, including the needs of scientific research projects, healthcare access, and the ability of patients to pay for treatment.

I aim to show that, if the internal logic of experimental clinical interventions cannot be explained in satisfactory terms of the in/externalisation of factors in the interest of the research and the patient (population), it may well cover up controversial aims, including the pursuit of profit at the expense of patients. By avoiding narrow bioethical approaches, we may be able to start mapping the large grey area between idealised scientific research and demonised stem cell tourism. A focus on how local factors are dealt with in an international context can help nuance the binary of RCTs and SCE (see Table 2), and enable us to understand why ‘unethical’ stem cell applications are ‘acceptable’ to some.

Social-science writing critical of RCTs problematizes the ways pharmaceutical companies and research institutions operate. One of the most scathing points of critique has been that RCTs proceed from idealised circumstances to further scientific knowledge, without sufficiently taking into account the local conditions in which trials take place (e.g., Will and Moreira, 2010; Rajan, 2006; Petryna, 2009; Mirowski and Sent, 2002; Fisher, 2009; Dumit 2012). By externalising local variability, the medicine resulting from expensive RCTs may become unsuitable for local use (Zwarenstein and Oxman, 2006; Montgomery 2012), while its adherence to ‘universal regulation’ may delay or change the direction of research.

But, in fact, some RCTs include local variability in the logic of clinical trials, comparing the effectiveness of research over a number of localities, internalising relevant difference into the trial as variables. RCTs do not just test safety and efficacy, but increasingly aim to observe the social functioning of treatments and set priorities for spending (Will and Moreira, 2010). As such, clinical trials can result in clinical interventions appropriate to ‘local daily life’ rather than the fabricated ‘ideal’ conditions of universal applicability. Such clinical trials tailor-made to the circumstances of patients are also referred to as ‘pragmatic clinical trials’ (Patsopoulos, 2011). The struggle to make RCTs more ‘relevant’ to real world problems and populations requires researchers to take into account institutional settings and to accommodate variation among the circumstances of patients (Will, 2007). The work by Steven Epstein on the properties and designs of AIDS in the 1980s (Epstein, 1996) exemplifies how new approaches can accommodate the demands and circumstances of patients to hasten results and distribute potential benefits. In the context of stem cell research, too, we observe a trend of global patient mobility and local patient demands shaping and facilitating internationally unaccepted forms of experimental stem cell therapy provision (Chen and Gottweis, 2013; Salter et al., 2015).

In fact, over the last few years, new forms of regulation have developed that allow ‘early’ clinical interventions. For instance, in South Korea and Japan, it is now possible to start conditional marketisation of stem cell products that have only been through limited safety and efficacy testing (KFDA, 2010; MFDS, 2013; PMDA, 2014), while in the USA and EU, regulatory spaces have been made available for the early clinical testing of ATMPs (US FDA, 2014a, 2014b, 2014c; EMA, 2014; MHRA,

2014). It is, however, stem cell interventions that are not subject to effective regulation that have been under heavy scrutiny, and an insistence on the implementation of the standard ethics of idealised clinical trials has incapacitated translational research in LMICs, such as China and India (Rosemann and Sleeboom-Faulkner, 2016; Bharadwaj, 2013). Although discouraging regulatory provisions have been in place in both countries (ICMR-DBT, 2012, 2013; Sui and Sleeboom-Faulkner, 2015), life scientists have created alternative ways of conducting research and responding to patient demands at the same time. Internalising local conditions with respect to regulation, expertise, healthcare, patient demand, regulatory oversight, and laboratory resources, researchers have set themselves various purposes, including research, consumer satisfaction, profit and clinical experience, whereby it has been unclear which aims, or combinations of these aims, have been prioritised.

Using the example of Beike Biotech (People’s Republic of China [PRC]), I will illustrate how a broader notion of ethics based on the ability to internalise and externalise (in/externalise) local factors can improve our understanding of the bionetworking that underlies clinical stem cell interventions.

1.3. Method and aim

‘Western’ discourses on the acceptability of clinical stem cell interventions often focus on the themes of payment, ethics and scientific evidence. Thus, asking patients for payment for clinical stem cell services and products that are not recognised by the international stem cell research community, stem cell intervention without independent research and ethical oversight, and providing stem cell interventions unsupported by scientific evidence, are regarded as unethical (Kiatpongsan and Sipp, 2009; Lindvall and Hyun, 2009; Gunter et al., 2010). To examine the application and relevance of these criteria (payment, ethics and scientific evidence) in China, in July 2012, November 2012, and March 2013, I asked 43 medical professionals, life scientists (20), medical doctors (14) and ethicists (9) for their views on the acceptability of the stem cell therapy provision services by Beike Biotech, a company widely criticised for charging exorbitant prices for unproven stem cell therapies. When told that in the eyes of foreigners Beike Biotech engages in unethical practices, the 18 interviewees that had not lived abroad showed surprise. Only those that work in both China and the US or had been abroad for over a year found Beike ‘unethical’, for reasons of charging high fees, for using unproven and unauthorised therapies, and for not having open patient records.

There is great variety in quality among stem cell research centres and therapy providers in China, and it is not easy to gauge whether therapies are evidence-based, whether patient fees cover costs or constitute profit, and whether a lack of research oversight means that unacceptable research is taking place. Nevertheless, reports exist about clinics that provide injections of cells of unclear provenance for steep fees and without scientific records for diseases widely believed to be incurable. These so-called ‘rogue’ clinics are usually contrasted with clinics that, as part of large-scale registered clinical trials, provide injections of precisely documented cells in a clinical study without charging fees. Using the notion of bionetworking, which presumes a connection between the production of scientific knowledge regarding life and a moral economy that involves weighing political, economic and cultural values, this article shows that most treatments can be found in an ethically grey area of stem cell experimentation combining research and treatment in various forms. To do this, first, I have analysed interview materials collected from 2012 to 2013, and, second, using the theoretical notions of in/externalisation, I have analysed the ‘grey area’ of the entrepreneurial aspects of stem cell interventions under different conditions and in different settings.

The interviews were analysed by repeated readings, thematic content analysis, and the identification of significant examples, using the abductive method (Timmermans and Tavory, 2012). By analysing the

Table 2
The grey area and the binary

	RCT	Grey area	SCE
Reliability	Bona fide	This area is not a neat combination of the merits of RCT and demerits of SCE, as they form an illusive binary.	Rogue
Quality	GMP, GLP, GCP		Unsure
Research ethics	Informed consent, IRB	Instead, we need to examine the ways in which local factors enable research to take shape through bionetworks.	Dishonest, no oversight
Scientific results	Generalizable		Unscientific
Benefit	All humanity		Exploitative
Procedures	Scientific protocol		Experimental
Knowledge	Universal		Inadequate

Table 3

A hypothetical research ethics continuum.

The binary between Random Control Trials and Stem Cell Experimentation					
Snake oil	Stem cell experimentation against payment	Compassionate treatment	Hospital exemption (EMA)	Conditional marketing approval before evidence (post-marketing data collection requirement)	Randomised clinical trial (Phase I–IV)

different views on the practices of the stem cell research and services provided by Beike Biotech, I argue that most stem cell interventions take place in a large grey area, in which narrow notions of ethics (i.e., treatment provided is based on scientific evidence, experimental treatment requires no payment, any treatment is provided under ethical oversight) are blurred with and supplanted by broader notions of ethics, co-determined by estimations of socio-economic, political and cultural understandings of risk and benefit. By probing into the externalisation and internalisation of local factors influencing both stem cell research and therapeutic products, I aim to introduce a new dimension to the appraisal of the 'ethicity of research'. In doing this, I intend to broaden the basis for understanding what is viewed as acceptable stem cell therapy.

After a brief discussion of different forms of stem cell experimentation, I will introduce in detail the in/externalisation of local factors in clinical stem cell interventions, before introducing the case of Beike Biotech. The case study is followed by a discussion of the applied method and its shortcomings and a conclusion. The research has received ethical certification from the ethical review board at the University of Sussex.

2. Distinguishing between forms of stem cell experimentation

Awareness of clinical stem cell applications as bionetworks focuses our attention on the entrepreneurial aspects of research finance (e.g., research funding, science investment, treatment fees), research policies (e.g., regarding standards, expertise, regulation, research data) and life values (e.g., values pertaining to health, bioethics, distributive justice) involved in life science innovation.

Experimental research that strictly follows scientific protocol, such as the four-phased, double-blind, randomised control trial with control groups, is designed to meet the standards of the world's leading peer-reviewed international scientific journals. The general validity of the RCT would make these trials universally repeatable and applicable. These kinds of trials are extremely expensive, not in the least because they need to meet the highest standards of GMP, GLP and IRBs, to be conducted by trained personnel, and have supervisory mechanisms in place to work according to authorised scientific protocol. Such RCTs are thought to be 'scientific evidence-based' and, ultimately, most beneficial to patients. However, wherever the intervention takes place, in practice many of the formal rules for clinical application and the 'patients' derive from high-income countries (Hunt and Khosla, 2010; Nwobike, 2006).

The research ethics of translational stem cell research and stem cell therapies are difficult to delineate in a consistent manner. I started out to explore this question using a 'research ethics continuum' ranging from 'rogue' to 'bona fide' stem cell applications, with RCTs as one extreme and 'snake oil' applications as the other Table 3:

Although helpful in the European context, such a continuum can also be misleading. For, what we call 'rogue' practices can become acceptable depending on the context in which they occur. In the case of patients with severe, intractable diseases, 'patient-driven experimentation' is performed in hospitals around the world. In cases where innovative cell products involve the testing of new procedures or drugs, regulatory provisions can be made. For example, doctors in Europe can now make use of the 'hospital exemption' (EMA, European Medicines Agency, 2010), while doctors in the US can test new treatments using the 'compassionate use programmes' (Moynihan, 2012). But all of these clinical stem cell interventions are required to follow scientific protocol, independent review by an Institutional Review Board (IRB), and ethics

procedures. In the case of the hospital exemption in Europe, experimental treatment forms part of the research framework in the form of a 'pilot-study'. Although these studies aim to systematically collect data, they are required to prioritise the welfare of the patient. In some countries, such as Spain, the number of patients involved can amount to hundreds of patients, while others only allow 10 (interview F, Leiden, April 2012). These forms of experimental treatment require doctors to weigh the benefits/costs of the new treatment against those of all other treatments available to the patient.

Another form of experimentation takes place in the context of what is often referred to as 'stem cell tourism' (Song, 2010), where clinics provide stem cell therapies for a wide range of serious diseases for high fees (Lindvall and Hyun, 2009; McMahon and Thorsteinsdóttir, 2010). Especially where there is little regulatory oversight of 'scientific' stem cell research practices, therapies may be applied with or without quality control and at all stages of the disease. Routine use of treatment procedures makes the practitioners of this form of profit-driven therapy highly experienced in the handling and the banking of cells, and the treatment procedures employed. Providers can use this work experience to claim expertise in clinical stem cell procedures, including those that are not accepted by the prestigious scientific journals. As exemplified in the case study of Beike Biotech, discussed below, such providers have begun to set up databases (planned or post-hoc) and gather material to examine the safety and efficacy of the therapies.

Ethical research is important for the safety of patients and the protection of the reputation of scientists. But the ethicality of stem cell experimentation is difficult to gauge in universal terms of treatment fees, ethical oversight, and scientific evidence used in the literature (Lindvall and Hyun, 2009; Gunter et al., 2010). This is because practices such as financial payment for medical interventions, using 'experimental therapy' as regular therapy, and the acknowledgement of possible patient benefit from experimental research are accepted in large parts of the world.

First, financial contribution to treatment is a conventional practice, also used in countries providing first-class healthcare. Thus, pilot studies for experimental treatment usually do not charge fees, but can ask for a contribution to the direct cost of the therapy (e.g., hospital bed, medicine and nursing) and insurance. For instance, in Japan patients pay for the basic costs of new drugs that have not passed the PMDA yet, and in the USA, the Code of Federal Regulations (CFR) 312.8 allows charging for investigational drugs under IND (USA GPO, 2012).

Second, in many countries clinical trials, which are also experimental, are regarded as a realistic healthcare opportunity, despite the lack of evidence of the efficacy of medical interventions. Thus, in countries with low standards of healthcare provision patients may view foreign experimental medicine as their best option, even when risks are involved that are unacceptable elsewhere, and even if medicines are not guaranteed after the trial.

Third, clinical trials may have adverse effects that require family care when the RCT does not take responsibility. Thus, some RCTs address national insurance schemes first in case of adverse effect, or fall back to care by family members when no hospital care is available (personal communication, IRB member in a hospital in Suzhou, China).

Finally, some providers of stem cell interventions are more seriously interested in research results than therapy outcome, while others are not interested in either. Awareness of this 'risk hierarchy' makes scientists more tolerant of some than other forms of 'rogue' therapy provision. Thus setting up GLP/GMP clinical trials of considerable risk without government permission may be regarded as less harmful

compared to driving patients into the arms of ‘rogue’ stem cell interventions (interview P, R, D March 2013; M, B, K July 2012).

These observations show that local circumstances and diverging healthcare contexts put into perspective the ethics criteria associated with idealised RCTs. There are also other, more general, reasons why the ethical appraisal of stem cell interventions cannot be defined in universal ethical terms.

First, scientific appraisal can be problematic, due to dissent among experts and their competing interests (Bianco, 2013; Centre for Bionetworking, 2014). When investigating plans for clinical studies, most governments find it hard to know which camps of scientists are the ‘most scientific’ or reliable. Among scientists in China there are those who support relaxed guidelines for translational medicine and others who insist on strict legislation. This situation is complicated by the systematic pressure exerted by sceptical experts who lobby for investment into public health or epidemiology (interview public health expert S, July 2012, Shanghai).

Second, patients want cures, independent of whether they are achieved through scientific knowledge, fluke, placebo or alternative treatments. To patients that cannot afford or find alternative healthcare in their country, commercial or experimental stem cell therapies may be their only option – especially if they see this as a chance for a higher quality or extension of life. A growing group of patients argues that any positive effect, even if the result of a placebo, and even if short-term, is preferable to no intervention (Chen and Gottweis, 2013).

Third, many patients do not think that paid-for treatment is automatically unethical. Although making profit using experimental medicine is unethical according to some, many patients understand that those providing commercial stem cell interventions do not necessarily regard patients as a mere source of profit. Rather, they need to maintain the viability of their enterprise to help patients (personal communication spinal cord injury patient, Nov. 2013).

Fourth, both patients and scientists acknowledge that experiments are needed for the advancement of science, but different locations organise these in different ways. Thus, the hospital exemption in the EU and compassionate treatment in other countries are mechanisms that allow trying out innovative treatments on a limited number of patients. Many researchers regard small-scale studies as expedient to yielding data of, for instance, innovative stem cell-based treatment for a complex and multi-systemic condition such as Parkinson’s Disease as preparation of large-scale clinical trials (Hyun, 2010). Such experimental spaces are also claimed in China (interview P, March 2013).

Although conditions of poor healthcare access lead patients to opt for risky treatment, it is also true that patients from HICs and wealthy people in LMICs without conventional treatment options flock to the same stem cell therapy providers. In addition, there are patients that have invested their life savings (and more) into the desired intervention. The patients go on a ‘stem cell pilgrimage’ (Song, 2010) despite warnings given by doctors and placed on the websites of the International Society for Stem Cell Research (ISSCR, 2008) and the International Society for Cell Therapy (ISCT, 2015) guidelines. It is clear, then, that understanding the provision of stem cell interventions requires an approach that analyses the reasons for provision and demand together.

To appreciate the workings of the bionetworks in which stem cell experimentation operates, rather than judging it by a narrow approach to bioethics, commercial aims, and research oversight alone, it is important to understand the healthcare needs of patients and the infrastructural resources available to populations. Ethics oversight, fee-payment and scientific evidence are only some of the aspects relevant to the exchanges between patients, doctors and life scientists, which are better understood in the light of the globalisation of the healthcare industry in interaction with the ways in which localities aim to meet local needs.

3. The internalisation and externalisation of local factors

The binary of RCTs and SCE blinds us to the bionetworks that combine elements of both in clinical applications. The clinical interventions of RCTs would follow ‘scientific’ protocol to improve the state-of-the-art, and ultimately to create medical products that can save people’s lives. The ethicality of RCTs has however been queried, as research in LMICs requires making adjustments to field sites through the externalisation of local factors that influence the protocol of a clinical trial (Will, 2007; Geissler et al., 2008: 705; Rothwell, 2005). Thus, a multi-centred, randomised stem cell trial for a certain non-communicable disease in a developing country needs to take into account characteristics of the patient populations and the research infrastructure. The other extreme of the binary, SCE, would exploit desperate populations by charging high payments for unproven stem cell interventions, making use of the vulnerabilities and features of the incurable, such as their desperation, naivety, lack of healthcare access, and wealth. In terms of the internalisation of local factors, these features could translate into the business prospects of ‘rogue’ stem cell interventions.

But a closer look at the internalisation and externalisation of local factors sheds light on the significance of ‘ethical oversight’, ‘fee payment’ and ‘scientific evidence’ in therapy provision, and yields insight into the process of the value realisation of clinical stem cell interventions as bionetworks. The life scientists interviewed were asked about the kinds of populations important for recruitment to test clinical stem cell applications in terms of the ‘features of patient populations’ and the ‘biomedical infrastructure’ needed (summarised in Table 4). The reasons for and the priority of their interest in the features of a particular patient population and the available research infrastructure varied greatly, and were dependent on interviewees’ emphasis on the importance of research, therapy, or both, and on their views on the availability of resources. Below I explain this in terms of the in/externalisation of local factors.

3.1. Externalisation

To realise optimal research conditions, interviewed life scientists had various priorities: a location with advantageous regulation, a suitable patient disease pool, skilled collaborative partners of good reputation, certified scientific institutions, and the public acceptability of the research. Various interviewees mentioned that, in some infrastructures, the research participants might require pre-treatment, simulating the standardised health conditions of ‘first world countries’, in preparation for the trial: after all, final products will need to reach high-demand markets. Thus, to optimise standard treatment, the participants would need to be precisely instructed (language; education) about the sanitary conditions (hygiene; diet), duration of the treatment (family circumstances), and its costs (insurance; transport; time off work or away from home).

There was awareness among most interviewees that, if and when medical products result, they might not benefit the tested population, as after the trial the population is expected to revert to its pre-trial lifestyle. Thus, even if the cost of the medical intervention would be met, the tested population may require sanitary conditions, hygiene, nutrition, knowledge, time and transportation normally not available in their everyday lives. The concern about being in the right condition to receive treatment is not just associated with RCTs, but with all modes of clinical research that require human research subjects to adopt substantial lifestyle changes, whether RCT, small-scale investigative studies, compassionate interventions, or pay-for-treatment studies (which, in addition, involve large payments, new medical regimes, suitable living environments and employment, and follow-up treatment). The availability of continued treatment or treatment for members of the tested population, interviewees pointed out, cannot be taken for granted even if financial support is available.

Table 4

The local factors mentioned by life scientists as being important to patient recruitment for clinical research (in order of frequency mentioned):

Relevant features of patient populations		Relevance
1. Health conditions		Rarity; availability of other options
2. Wealth		Affordability of treatment
3. Insurance coverage (national/private)		To pay for adversities
4. Prognosis		Treatment survival chances; demand for end-product
5. Age		Treatment survival chances
6. Availability alternative treatment options		Treatment choice
7. Employment		Need to take time off; ability to pay
8. Sanitary conditions at home		Conducive to the intervention
9. Language ability, schooling		Medical regimen, and comfort
10. Availability/affordability of transport		Enhances understanding instructions (If travel is necessary)
11. Diet and availability of nutrients		Conducive to the intervention
12. Family situation		After-care; support; children;
13. Religious/national/ethnic identity factors		Care and payment issues
		Issues of belief, gender, trust, care
Important aspects of the research infrastructure of a country/region	1. Regulation of cell products and their clinical application	Need for permissions, equipment; ethics
	2. Regulatory bureaucracy	Time and payments involved
	3. Research funding	Affordability of research, equipment
	4. Patient pool	Recruitment
	5. Availability of medical, linguistic, scientific, and technical expertise;	To explain the research to population, administer interventions, and maintain equipment
	6. Reputation of research and medical institutions	Trust of population and acknowledgment of scientific community
	7. Certification laboratories and clinics	Conducive to trust and reputation
	8. Sensitivity of the media	Risk scandal; advertising opportunity

The evidence-based science orientation of RCTs was also criticised for creating medical products that are unaffordable due to intellectual property rights (iPR). However, medical products generated outside of RCTs can also carry iPR. For instance, Beike Biotech, who does not organise classical RCTs, promotes its 20 patents and AABB certificate (Beike, 2014a) in advertisements and in its negotiations with provincial biobanks and hospitals. And, Beike's stem cell products can be just as unaffordable, as will be illustrated below.

3.2. Internalisation

The scientific basis of the research may be affected by the social and physical circumstances in which it takes place, for it is not always possible to externalise the 'undesirable' conditions that are part and parcel of the field site (Montgomery, 2012). In such cases, they are unavoidably internalised into the research. This was clearly recognised by the interviewees engaged in clinical trials (P March 2013; H, O Nov. 2012), who indicated that research participants bring into the research their particular social conditions related to healthcare, diet, medicine, physiological idiosyncrasies, hygiene, and attitudes that shape the reaction of the experimental body, and which may influence the results of experimental research. In other words, the undesired internalisation of local conditions may be unpreventable, and introduce bias into the research, as is the case with pragmatic clinical trials (Patsopoulos, 2011; Sugarman and Califf, 2014).

Some local factors, including healthcare access, regulatory regimes, and the socio-cultural background of various populations, are ambiguous, as they can seem to be external to clinical stem cell interventions. They are nevertheless internalised for various reasons. For instance, the socio-cultural background or 'ethnicity' of a population can be pertinent to the 'scientific logic' of clinical research when the population is thought to be sensitive to certain chemical components in drugs. In other cases, ethnic background can be expedient to lucrative clinical stem cell research ventures when internalised strategically. Thus, if a group of patients with a certain social or ethnic background is known to lack healthcare access (cf Medpace, 2013), it may become the target of patient recruitment (interview, Q July 2012). In such cases the internalisation of ethnicity serves profit-making.

Some interviewees criticised 'irresponsible' clinical stem cell interventions as 'experimentation' for ignoring the particularity of disease conditions, such as when the same stem cell intervention is applied for both Parkinson's and Huntington's Disease (N, Z Tianjin, Nov. 2012). In this case, the variability of patients' conditions remains 'unmarked'. However, the failure to mark the particularity of a potential patient population also occurs in RCTs, such as when the size, ethnicity, weight, age and other physiological features of patients are not taken into account (Leichleiter, 2014). Participants in RCTs may also be selected for their particular characteristics, be it genetic make-up, medical naivety, lack of alternative treatment, or absence of strict regulation in the country the RCT takes place (Sleeboom, 2005; Pomfret and Nelson, 2000; Petryna, 2007, 2009). Even though in such cases patients may not have to pay for participation, they take a considerable medical risk and have no guarantee that any potential medical products will become available to them.

The reasons for the internalisation and externalisation of features of the targeted patient population and its environment vary, and are inherent to the bionetworks they are part of. Aspects of experimental conditions are internalised not just because they are hoped to contribute to the state-of-the-art or to benefit patients, but also because other interests play a role, such as reputation, market-share, profit, or contact networks. Similarly, knowledge of the patient's healthcare access, insurance, education, religious belief, wealth, living conditions and family situation may all be valuable for patient recruitment purposes, while knowledge of a country's healthcare system, regulation, patient pool, communication system, expertise, jurisprudence, insurance system and science policy are important to the location of stem cell clinics. Interviews made clear that such knowledge of localised conditions underpin the organisation of clinical stem cell application in general, including in the work of clinical research organisations (CROs), state hospitals and commercial stem cell applications.

4. Why Beike Biotech is 'acceptable'

By interpreting Beike Biotechnology as a bionetwork that internalises and externalises local factors, I explain why many Chinese life scientists refer to Beike Biotech, which is often referred to as 'unethical', as an 'acceptable' provider of stem cell interventions. This case shows how Beike's bionetworking activities enabled it to gradually evolve from being able to in/externalise only a few factors to being able to selectively pick which factors to in/externalise. Before ethically adjudicating the activities of clinical stem cell providers, understanding the stem cell interventions as part of bionetworks can help us to explain more constructively why unauthorised stem cell interventions are used in some locations but not in others.

Beike Biotechnology was set up in July 2005 in Shenzhen by Xiang Hu (Sean Hu), and the company specialises in stem cell research, clinical translation, and technology support services of adult stem cells. Since 2005, Beike has provided stem cells for clinical application to over 16,000 patients suffering from neurological, hepatic, vascular and other conditions (Beike, 2014a). After receiving his PhD from Columbia University in 2001, Xiang Hu returned to Zhengzhou University, his alma mater in China, where he focused on translational research for severely disabled patients. After he attracted capital from Hong Kong Science & Technology and Qinghua Universities, Hu decided to set up his company in Shenzhen in the South of China. In 2006, the Shenzhen government invested 900 k RMB (US\$4m) into its industrial zone, to which it invited Beike to set up its headquarters, and, in 2009, Beike opened its Stem Cell Regenerative Medicine Industrial Complex in Taizhou, calling it "the world's largest stem cell storage and processing facility" (Beike, 2009). Beike set itself an international mission:

Beike is the world's largest stem cell provider focusing on the research, product development, and clinical translation of adult stem cells as well as immunotherapy. Our goal is to increase communication

with governments foreign and domestic to bring regenerative medicine to the world.

Before 2009, in China no official permissions were needed for clinical stem cell research and no rules guided the application of experimental stem cell therapies (Sui and Sleeboom-Faulkner, 2015). Until 2009, approximately one hundred stem cell companies and 400 hospitals had applied stem cell transplantation for clinical therapy against high treatment fees (Cyranoski, 2012). But in 2009 the Ministry of Health enacted the Management Measures for the Clinical Use of Medical Technologies, requiring permission for stem cell clinical application. Stem cells applications were ranked as 'category three' medical technology, entailing the possibility of serious ethical problems, and safety and efficacy issues in need of being proven by clinical trial, though the rules did not carry punitive measures. Although the media referred to the inadequate governance of clinical stem cell research situation sporadically as 'stem cell chaos', and various sets of regulation were introduced (Sui and Sleeboom-Faulkner, 2015), Beike Biotech continued to grow.

Nevertheless, it has been heavily criticised internationally. One critic said of Beike:

Beike is one of the biggest and baddest of all the companies that have made their millions selling untested, unregulated and uncontrolled stem cell injections to patients suffering from a wide range of serious diseases (Sipp, 2011).

But within China, Beike has also received much sympathy, if not support. Here I make use of interviews with life scientists and regulators to show why Chinese medical professionals and ethicists express confusion and surprise at hearing about the dominant image of Beike Biotech outside China as 'unethical'.

Beike itself organises international patient recruitment through agencies for stem cell tourism, and through websites, on which it collects information about the medical records of patients, their ability to pay, their insurance coverage, and their family situation (interviews 2012–3). Most of the providing hospitals are private, and are endowed with various levels of luxury and treatment methods to cater for patients of different means and taste (hospital visits in Beijing, Shanghai, Tianjin, Guangzhou, 2012–3). Staff at Beike Biotech said that they regard the fees for the stem interventions as 'similar to buying a car' (Interview D, March 2013, Shenzhen), but for many patients the 30–100 k RMB means a fortune. Beike employees justify prices in reference to the licensing fees that 'American' corporations levy from laboratories in China (ibid). At the same time, some Beike employees are dissatisfied that profits are invested into luxury items rather than into facilities for conducting research (Interview D, March 2013). Although Beike did not have Chinese Food & Drugs Administration (CFDA) permission to provide stem cell therapy, it continued conducting medical trials and providing stem cell interventions at least until my visit in 2013 (see, <http://clinicaltrials.gov>)¹ through collaboration with a range of hospitals, universities and local governments. The medical trials were partly financed by provincial governments and cities, and took place in private and military hospitals. Most are run in (high-ranking) third-tier hospitals by medical doctors (interview R, Guangzhou, March 2013), which are keen on increasing the number of private patients.

Although, as mentioned, articles critical of stem cell tourism have appeared in the Chinese media (Lue, 2013), Beike's scientific image is not usually disputed. Interview responses indicate that it is mainly the scientists that have part-time jobs abroad or have resided abroad for a prolonged period of time (over a year) who are aware of the poor scientific reputation Beike has outside China: not keeping medical records for outsiders to inspect, providing unproven therapies to patients, and taking advantage of the placebo effect, not publishing its results in international science journals of reputation (e.g., Lim, 2008; McCullough, 2008; Johnson, 2010; Tam, 2011; Brown, 2012; Chen and Gottweis, 2013).

The life scientists that find Beike's enterprise acceptable treat such views as false allegations by referring to Beike Biotech's website, articles and company events. This is a summary of their defence of Beike as acceptable:

- (1) Over the last years Beike has built up a rich experience of therapy provision, simultaneously engaging in collaborative research and clinical trial, which has led to the joint publication of articles in international journals such as *Journal of Translational Medicine*, *PlosOne* and *Stem Cells* (also see, Beike, 2013a).
- (2) In 2009 Beike was visited by President Hu Jintao and Premier Wen Jiabao, who praised Beike's scientific and therapeutic competence in comparison with the world's most renowned life science hubs (Anon, 2010).
- (3) As for the placebo effect, interviewees argued that if it is true that the scientific basis of stem cell therapies is not clearly understood yet, then it is also unclear whether or not any signs of improvement are attributable to any placebo effect (interview H, J, K 1, July 2012).
- (4) Although patient records have not been maintained in the past, Interviewee L said that they are being kept now, but cannot be opened for inspection by competitors and audit for reasons of iPR and patient confidentiality (interview M, July 2012). Those who want to know more were referred to Beike's website, which has patient case studies for the world to admire (Beike, 2012a).
- (5) Any queries about the provenance of the stem cells used in therapy are referred to the umbilical cord blood (UCB) banks Beike runs and its connection networks (Beike, 2012b). Collaboration with provincial governments in the management of provincial UCB banks and the state support it receives through grants and collaborations (Beike, 2013b) were cited in indicating Beike's reliability.
- (6) Interviewees referred to the world's 'highest certificate for blood banking' (AABB) Beike received in 2012 (Beike, 2012c).

It is clear that over the last 10 years Beike has undergone substantial changes. Its capacity to internalise factors has increased. Beike has moved from a situation in which it did not have sufficient capacity to make distinctions between the various conditions of patients, use clinical methods, write publications in internationally peer-reviewed journals, and provide rehabilitation, and it had little experience with the banking of stem cells and tissues and keeping patient records. Failing to mark patient conditions, methods and materials, Beike could not sufficiently externalise local factors to make its research 'universally valid and repeatable' through, for example, keeping patient records, testing drug regimes, training patients to observe medical regimes, and testing rehabilitation methods. Neither was it clear whether Beike internalised patient conditions to address research questions relevant to the particular patient populations it was targeting through pragmatic trials. It was only seen to internalise factors for lucrative purposes: patients' financial background, their lack of alternative treatment options, and their hope.

The fact that patients had to pay for 'experimental' interventions, most of the life scientists I interviewed in 2012 and 2013 did not regard as unethical per se. After all, therapies falling outside China's local healthcare provision lists were largely sold on a commercial basis, and total healthcare insurance coverage was rare. Patients were used to paying for private and authorised therapies. Furthermore, the practice of giving 'red envelopes' (bribes) to create goodwill is common (Yang, 2007); and, while patient choice of medical doctors/surgeons has become a right in China, many patients nevertheless pay extra. The observation that Beike's services attract 'foreign' patients, who until recently paid twice the amount Chinese patients did (interview D March 2013, Shenzhen), was regarded as further proof in support of the reliability of Beike's services. Considering that there were no other affordable healthcare options for most patients, and that established life science

¹ <http://clinicaltrials.gov/ct2/results?term=beike&Search=Search> (this search has been conducted on June 25, 2013). [Last accessed: July 2, 2013].

centres did not receive permission to start Phase I trials in stem cell applications (Xinhua, 2013), Beike, according to interviewees, was an obvious alternative, also for patients that do not suffer from life-threatening or intractable conditions.

Gradually, Beike's financial and research capacity has become a substantial force in China's regenerative medicine industry. A brief description of the evolution of one of Beike's stem cell collaborations with Drum Tower Hospital and Jiangsu University in Jiangsu, an important link in its stem cell network regarding the study of systemic lupus erythematosus (SLE), illustrates this. The bionetwork, which has evolved since 2010, shows how Beike's capacity to select its in/externalisation has increased dramatically (Beike, 2010). After years of experience with stem cell applications, the collaborative network formulated a clinical trial, which was financed by Jiangsu Province (US\$1.8 million) to develop clinical applications using mesenchymal stem cells from umbilical cord blood to treat SLE. A division of labour emerged, whereby Beike provided the facilities, equipment, management framework, and proprietary clinical stem cell technologies for the project, and Nanjing University Medical School's Drum Tower Hospital, experienced with clinical studies of SLE, took care of administering the human trials and enlisting of 200 patients, while Jiangsu University brought its biological research and development resources to the production and animal study phases to the project (Sun et al., 2010). In 2014, the group published their study results in, among others, one of Biomed Central's flagship journals *Arthritis Research & Therapy* (cf Wang et al., 2014). It had recruited forty patients with SLE from four clinical centres in China and infused them intravenously with allogeneic UC MSCs at specific times, firstly, to test safety profiles, and secondly, to test clinical response. Clinical indices, including Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, British Isles Lupus Assessment Group (BILAG) score and renal functional indices, were also taken into account. The article shows attention to safety, clinical response and relapse to an extent that Beike would hardly have been capable of before 2009. But due to a focus on narrow definitions of bioethics, these changes occurred unobserved. While in 2012 Beike's President Xiang (Sean) Hu was still criticised for being a Stem Cell Madman in *Entrepreneur* (see Note 2), in October 2013 Beike submitted the Investigational New Drug (IND) application to register their UC MSCs for clinical use to the Guangdong Province FDA and was accepted. In March 2014, the CFDA officially accepted the IND for review for clinical use (MarketWatch 2014).

This case-study of Beike Biotech shows why it is important to know how and why local factors are in/externalised into the clinical research. It allows us to discern the logic of 'acceptability' in its local context, such as

- Whether patients pay fees to maintain the work of doctors and researchers and exorbitant profits that disappear into the pockets of individuals;
- Whether patients are told fairy-tales or whether they are given realistic data on the therapeutic prospects;
- Whether interventions are uncontrolled try-outs or whether they are part of larger-scale research;
- The source of certifications and the quality of publications (e.g., whether a company has its own journal or publishes in widely-known journals; whether life scientists are main authors or free-riders on articles; whether certifications are bestowed by suppliers or well-known institutions with authority).

The relation between local context and the bionetwork changes over time: the chance of its configuration can help us understand the drivers of clinical research applications and whether they fit the purported purpose.

Viewing Beike as an entrepreneurial bionetwork enabled the observation of a broad range of activities around the provision of stem cell

intervention and the development of stem cell products. Beike started out using identical stem cells for many different conditions using similar methods: it internalised patient demand, including the various payment abilities and origin of patients by catering for their circumstances, and it internalised a large range of diseases by applying methods and procedures indiscriminately. Gradually, however, it built up experience, archives, and scientific capacity that improved its ability to subordinate its internalisation efforts to a systematic approach requiring externalisation. Standardisation of patient records and intervention outcomes made possible the diversification of scientific protocol, while learning enough about treatment effects to know when not to treat led to the exclusion of untreatable patients and the establishment of standard treatment regimes of rehabilitation. Beike's efforts were made possible financially through the fees of patients and funding application efforts by scientists, which led to lucrative collaborative arrangements with hospitals, universities and governments, as a result of which Beike has become a major player in umbilical cord banking, has experience expertise on stem cell processing, and has accumulated relations with universities and hospitals that now possess extensive knowledge of stem cell applications. Whether these constitute the world's state-of-the-art is an important question from a scientific point of view, but perhaps not most relevant to companies and institutes that wanted to improve their start-position by catching up.

5. Discussion — the complexity of local factors and the grey area between RCTs and SCE

Observations of the in/externalisation of aspects of experimental field sites, including data on the patient population and their living conditions, can help indicate whether experimentation contributes to research efforts and the benefit of patients. In the case study above, I have argued that, if the internal logic of experimental clinical interventions cannot be explained satisfactorily in terms of the in/externalisation of factors in the interest of the research and the patient (population), there is a possibility that it serves controversial aims, including the pursuit of profit at the expense of patients. This method is much broader than the narrow approaches to ethics used thus far, and a step forward in an attempt to create transparency in the large grey area between RCTs and SCE. To find out whether taking into account local factors is conducive to desirable stem cell interventions, we need to know to what purpose local factors are mobilised, i.e., which aspects of patients and infrastructures are relevant to the internal logic of an experiment. Nevertheless, this method has its limitations.

First, the internalisation of patient characteristics such as environment, diet, genetic make-up, age, gender and weight can take place for various reasons. For example, the logic of a clinical trial may require information on body weight, ethnicity or gender to determine the most appropriate drug dosage. But clinical trials might also include criteria for age and body-weight with the aim of extending a patent, even though the additional knowledge gained from the trial is of no scientific significance or relevance to the patients (Angell, 2004). In still other cases, the criteria for diet, genetic make-up, age, gender and weight may be seen as essential for the introduction of a therapy into a country, an argument that Japan has used in negotiations with ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Kuo, 2007). It is important, then, to know whether the reasons for including epidemiological, social and cultural criteria are political, financial, medical, or research related.

Second, views on the effects of stem cell intervention using MSCs are contested. Some stem cell scientists accuse providers of failing to distinguish between disease profiles, such as Alzheimer Disease, diabetes, Parkinson's Disease and Spinal Cord Injury (SCI). Some scientists regard the safety and efficacy of MSC therapies as unproven and therefore unethical if commercially provided (Bianco, 2013; Bianco and Sipp, 2014; Paterlini, 2014). Providers justify their interventions by referring to the ability of MSCs to secrete paracrine factors and cytokines that

regenerate healthy tissue (interview, Y, Nov. 2012). But, according to a scientist who oversees a well-equipped lab in Shanghai (interview L, Nov. 2012, Shanghai), it is by no means clear how many cells should be administered and by what method, where the cells go, and whether they home-in, transform or disappear. Other scientists, including some at Beike (interviews D March 2013; Y, Nov. 2012), say that the intervention has a short-lived effect (3–6 months at the most – interviewees Shanghai, Shenzhen, Beijing and Guangzhou). Internationally, the number of clinical trials using MSCs registered on the website clinicaltrials.gov, a US National Institute of Health database that provides patients, family members and the public with information about current ongoing clinical research studies, has increased, but the way MSCs work remains disputed. Thus, the use of MSCs in the treatment of Graft-versus-Host Disease (GvHD) was explained to me variously as fusion, transdifferentiation, and paracrine effect. In short, ‘the science’ is contested.

Third, there may be disagreement about the necessity of in/externalising local factors, as scientists might disagree about whether something is ‘particular’ and in need of externalisation. Thus, what are regarded as unsuitable diet, unsanitary conditions and clashing medical regimes might be ‘externalised’ using financial support, a ‘Western’ medical regime, nursing, antiseptic devices, and a pollution-free living space during the medical trial. But to local patients these ‘particularities’ may be part of an unquestionable daily life. These ‘particular’ conditions may need to be taken into account or be ‘internalised’ to the logic of the research plan, so that any resultant medical products will suit their way of living. Life-style factors (stress, housing, kinetic movement) and cultural factors (gender- and age-specific traditions, fasting, religious rites, conjugal habits) may have to be treated as ‘normal’ conditions for the treatment to ‘work’ under locally ‘normal’ circumstances. As for MSC interventions, rehabilitation therapy can be crucial to the efficacy of the intervention (Aoyama et al., 2015), requiring patients to maintain ‘normal’ daily activities. The question of whether environmental factors are internal or external to the logic of treatment may be decisive to catering for patient demands. Indeed, it is the question underpinning new research trials in China initiated by Beike and military medical institutions advertising their trials on clinicaltrials.gov.² To complicate the matter of ‘acceptability’ of stem cell interventions, clinicaltrials.gov itself has become suspect of legitimising irresponsible research (Piller, 2015; Clarke et al., 2010: 72).

6. Conclusion

During the first decade of this millennium a disjunction between the aims and means of biomedical interventions sharpened as a result of the globalisation of personal networks of scientists returning to LMICs. Chinese scientists that followed their education abroad, including Beike Biotech founder Xiang Hu, were trained in ‘Western’ laboratories and became well versed in scientific theory. When returning home, however, they landed in a very different institutional and regulatory environment, whereby the comparatively low standard of healthcare access and scientific provisions made an orientation on patients unavoidable, despite their research interests and activities. For over a decade now, an increasing number of translational stem cell researchers, such as those at Beike, have studied patient records post-hoc, and ventured to test scientific hypotheses on the basis of knowledge garnered from science journals and an increasing number of patient records. Thus, patient observations in combination with deductive reasoning have served to further knowledge in a pragmatic, experimental manner. Even what some see as educated guesswork may lack systematic data collection, the application of research/ethics regulation, and state-of-the-art equipment and conditions may be directed at developing into something that merits increasing ‘acceptability’.

In this article, I argued that there exists a large grey area between ‘bona fide’ RCTs and ‘rogue’ SCE, due to the narrow notion of ethics used in writings about clinical stem cell research and interventions. Rather than judging the acceptability of a stem cell intervention on the basis of ethical review, fee payment and scientific evidence, this article views all institutions that provide stem cell interventions as part of entrepreneurial bionetworks. The notion of bionetworking focused our attention on the entrepreneurial aspects of research finance, research policies, and life values involved in life science innovation. As illustrated by the case study of Beike Biotech, bionetworking activities pertain to the changing configuration of the in/externalisation of local factors, including features of disease populations and the environment, treatment demand, healthcare provision, wealth, regulation and state-of-the-art.

I invoked the case study of Beike Biotech to maintain that the use of narrow ‘Western’ standards for stem cell science is unsuitable for appreciating the variable conditions of stem cell science in LMICs, where many researchers are side-lined due to a lack of resources. Critics regard rebels such as Beike Biotech as unethical and greedy, as they use a commercial agenda in the provision of stem cell products. In this context, I made use of the notion of bionetworking to examine entrepreneurial and strategic activities in life science research and clinical applications to argue that life scientists, whether commercial or state supported, all have entrepreneurial agendas, although they play out differently. In summary, I showed that: if the entrepreneurial in/externalisation of local factors by an enterprise (be it RCT, commercial provider or state institution) is unclear, hidden or exploitative, there is reason to be critical of the clinical application Table 5.

I observed how local factors are internalised and externalised through bionetworking activities. *Externalisation* excludes local features and environmental factors of a population to enhance the universal validity of research application by adjusting the population or its environment; *internalisation* utilises local features and environmental factors of a population in a research application to enable the application of research products to particular populations. The externalisation of local factors apart from in RCTs also occurs in other kinds of clinical research application, such as in investigator-led clinical trials. The internalisation of local factors, such as those of healthcare, wealth, regulation, culture and hygiene, allows the application of a limited number of principles to a diverse population. This can yield clinical interventions for particular disease populations in both exploitative and beneficial ways. While some research projects have started to internalise (utilise) local factors to adjust the research to the needs of a particular disease population, the internalisation of particular features of local populations, such as its ‘medical naivety’, disease conditions, and despair can take advantage of the vulnerability of patient groups.

Examining how the in/externalisation of local factors underpin Beike’s development, I showed how ‘unethical’ forms of internalisation have various functions, such as yielding profit, clinical experience, research results and patient data. These same functions have enabled Beike to set up stem cell banks and scientific collaborations, conduct and publish research, and engage in collaborative research with universities and hospitals. Although this does not mean that the company behaves in a way acceptable to the ‘international science community’, the company does not just sell snake oil either. I have argued that, rather

Table 5

The strategic in/externalisation of local factors in medical trials to create biomedical products.

Local factors	Can be both in/externalised, e.g., healthcare, wealth, regulation, culture, disorders, hygiene, ‘medically naïve’ population
Internalisation	To adjust the research to the needs of a particular disease population (<i>beneficial</i>); to take advantage of the vulnerability of patient groups (<i>exploitative</i>)
Externalisation	To enhance the universal validity of research by adjusting the population (<i>beneficial</i> to the ‘dominant’ population; <i>exploitative</i> , if resulting medical products are not provided or suitable for the participating population)

² See <http://clinicaltrials.gov/ct2/show/NCT01393977>; <http://clinicaltrials.gov/ct2/show/NCT01929434>.

than just passing judgement, it is important to understand why and how local factors are in/externalised into the clinical research: to benefit the research, the patients, or for other purposes. The configuration of the connection between local factors and the in/externalisation activities in a bionetwork over time can shed light on the local rationale behind the acceptability of clinical research.

Rather than leading to a form of ethical relativism in the field of regenerative medicine, such improved understanding should alert initiators of the creation of global research and ethical guidelines that they will affect the clinical research activities of those who are excluded from their formulation. ‘Snake-oil’ providers can be detected globally, and are broadly condemned — there is no need for a formal ethical framework against these, just a legal one. However, if ethics and research guidelines are intended for global implementation, efforts are needed to include in the regulatory process scientists from parts of the world, whose practices may be frowned upon. This will require a more realistic understanding of the ‘large grey area’ of clinical stem cell research, and a reconsideration of the terms of global competition in regenerative medicine, a field widely perceived as fraught with ethically sensitive issues.

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